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(54) Title: HYDROPHILIC PRESSURE SENSITIVE ADHESIVE FOR TOPICAL ADMINISTRATION OF HYDROPHOBIC DRUGS

(57) Abstract

Novel hydrogel formulations useful as adhesive reservoirs for topical or transdermal drugs employ as the polymer base a crosslinked polymer or copolymer of 2-acrylamido-2-methylpropane sulfonic acid or a salt thereof. The gels are prepared from polymerizable compositions comprising: 20 % - 50 % of a monofunctional monomer component, at least 75 % of said component comprising 2-acrylamido-2-methylpropane sulfonic acid or a salt thereof, the balance being selected from the group consisting of acrylic acid, water soluble acrylic functional monomers and vinyl pyrrolidone; 30 % - 50 % of a glycol component selected from the group consisting of compounds of the formula: $HO-(C_2H_4O)_n-H$, $HO-(C_3H_6O)_m-H$ and mixtures thereof, where n is in the range of about 4 to about 16 and m is 1-4; between about 0.02 % and about 0.20 % of a crosslinking monomer; an amount of a free radical polymerization initiator effective for initiating polymerization of said monofunctional monomer and crosslinking monomer components; and a therapeutically effective amount of a topically or transdermally deliverable drug, at least about 60 % of said drug being dissolved in the formulation.

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HYDROPHILIC PRESSURE SENSITIVE ADHESIVE FOR TOPICAL ADMINISTRATION OF HYDROPHOBIC DRUGS

Field of the Invention

This invention pertains to adhesive matrix materials for transdermal or topical administration of medicines.

Background of the Invention

US 4,017,615, 3,888,995 and 3,592,930 pertain to ointment-like vehicle for corticosteroid drugs and the like.

References which disclose film formers as ingredients for topically administered dry formulations include US 2,973,300, US 3,214,338 and US 4,210,633.

Bandage-like devices for delivering drugs topically or transdermally are described in U.S. patents 3598123, 4191743, 4605548, 4655768, 4409206, 4286592, 4230105, 3948254, 3742951, 3734097 and 3731683. Such devices may include separate adhesion and drug reservoir layers.

US 3,536,809 discloses a mixture of a drug such as progesterone dispersed in a polyalkyleneglycol impregnated into a fabric strip which may be retained in the mouth to administer the drug through the buccal mucosa.

Considered more pertinent to the invention hereof are polymeric dispersion matrix materials which have skin adhesive properties and have a drug dispersed directed into the matrix.

In US 3,632,740 it is suggested to incorporate a drug such as a corticosteroid into a pressure sensitive rubbery adhesive layer on a flexible backing.

In US 4,292,301 there is disclosed a polymeric diffusion matrix said to permit sustained release of ephedrine, the matrix comprising a polar plasticizer such as glycerol or polyethylene glycol (MW 1000), polyvinyl alcohol, polyvinyl pyrrolidone and ephedrine.

US 4,470,962 discloses a polymeric diffusion matrix said to be capable of sustained release of a drug comprising glycerol, polyvinylalcohol, a water soluble polymer with hydration sites, a drug dispersed therein and water.

US 4,307,717 and 4,675,009 describe bandage materials which include a backing element and a substrate comprising a matrix material comprising a solid phase formed of a polysaccharide or certain synthetic polymers and a liquid phase consisting of a hydric alcohol, carbohydrates and/or proteins in an aqueous solution. The matrix material also contains a medicament suspended or dissolved therein.

US 4,593,053 discloses polyvinylalcohol/polyvinyl pyrrolidone based gels with non-syneresing adhesive characteristics. In one embodiment the gels contain an ionic drug which can be iontophoretically delivered. Tacifiers such as poly-2-acrylamido-2-methylpropane sulfonic acid may be added to the formulation at levels of 2% - 20%.

Hydrogel materials based on polymerized 2-acrylamido-2-methlypropane sulfonate salts are known as electrode materials from US 4,391,278 and US 4,768,523. In US 4,391,278 a tape electrode is disclosed which includes a gel comprising polymerized 2-acrylamido-2-methane sulfonic acid or a salt thereof, water and/or an alcohol to give electrically conductive, flexible skin adhering properties. All of the example formulations employing an alcohol utilize glycerol although propylene glycol and sorbitol are also mentioned as useful.

Summary of the Invention

The present invention pertains to novel hydrogel formulations useful as adhesive reservoirs for topical or transdermally administered drugs. The formulations employ as the polymer base a crosslinked polymer or copolymer of 2-acrylamido-2-methylpropanesulfonic acid or a salt thereof, preferably the sodium salt.

The invention also pertains to polymerizable formulations, curable to produce such adhesives on a backing, in particular such formulations comprise a formulation comprising:

20%-50% of a monofunctional monomer component, at least 75% of said component comprising 2-acrylamido-2-methylpropane sulfonic acid or a salt thereof, the balance being selected from the group consisting of acrylic acid, water soluble acrylic functional monomers and vinyl pyrrolidone;

30%-50% of a glycol component selected from the group consisting of compounds of the formula

$$HO\text{-}(C_2H_4O)_n\text{-}H,$$

$$HO\text{-}(C_3H_6O)_m\text{-}H$$

and mixtures thereof, where n is in the range of about 4 to about 16 and m is 1-4;

between about 0.02% and about 0.20% of a crosslinking monomer;

an amount of a free radical polymerization initiator effective for initiating polymerization of said monofunctional monomer and crosslinking monomer components; and

a therapeutically effective amount of a topically or transdermally deliverable drug, at least about 60% of said drug being dissolved in the formulation.

In the preferred embodiment the drug is a hydrophobic drug. Most preferably the compositions are curable by UV irradiation.

The invention also comprises cured gels produced from formulations as described above, particularly of a laminate on a suitable backing material to form an adhesive bandage or patch.

Description of the Figures

Figure 1 is a graph comparing migration results of hydrocortisone from gel adhesive materials of the invention against several commercial hydrocortisone containing ointments and creams.

Figure 2 is a perspective view of a bandage employing a drug containing gel adhesive of the invention.

Detailed Description of the Invention

The polymerized matrix gel material of the invention is tacky, light to moderately adhesive and leaves little or no residue on the skin when removed. That is, its cohesive strength is sufficient to overcome its adhesive properties.

Suitably the polymerized matrix gel material is used as a thin layer on a flexible backing material to produce an adhesive bandage-like structure. The preferred bandage, shown in Figure 2, is a laminate structure 10 having a flexible backing material as the top layer 11; a supported gel matrix layer 12 which comprises the cured drug containing adhesive gel 13 and includes in the central portion thereof a reinforcing fabric 14; and a bottom peelable protective layer 15 which is removed when used. A backing material which is preferred for its moisture transmission properties is a 2.5 mil flexible ether type polyurethane. However, an elastomeric polyester such as Hytrel™ or a polyethylene film material may also be used. Useful reinforcing fabrics are spun bonded polyester or polyamide fabrics about 5 mils thick having a weight of about 0.4-1 ounce per square yard. The central gel and reinforcing fabric layer is suitably about 0.05" - 0.25" thick, preferably 0.15" thick. The bottom peelable release layer, which is suitably about 5 mil thick, may be a polyester such as Mylar™ polyester, various copolyesters, optically clear styrene or other suitable release sheet material.

The polymerized gels of the invention are based on a monofunctional monomer component which is predominantly (i.e., at least about 80% by weight) 2-acrylamido-2-methylpropanesulfonic acid or a soluble salt thereof. The acid monomer is sold by Lubrizol Corp. under the trademark AMPS®. Most preferably the base monomer is the sodium salt ("Na AMPS").

This monomer will polymerize free radically with common initiators, including peroxy compounds and UV photoinitiators. The monomer is capable of polymerizing with crosslinking monomers in the presence of water and/or alcohols to produce shape retaining gels which are flexible and adhesive. Suitably the NaAMPS monomer is employed as a 40-60% solution in water.

The 2-acrylamido-2-methylpropanesulfonic acid monomer is suitably copolymerized with minor amounts of additional water soluble monofunctional monomers such as acrylic acid, vinyl pyrrollidone or water compatible acrylic functional monomers, particularly water miscible acrylamide functional monomers. Most preferably it is copolymerized with acrylic acid, which suitably comprises up to 25% of the total monofunctional monomer, preferably about 6% - 18%.

A small amount of crosslinking monomer is also incorporated into the inventive formulations. Crosslinking monomers have 2 or more copolymerizable groups and may include prepolymer compounds with the requisite functionality. Such monomers include di and poly acrylate or acrylamide functional compounds. Particularly preferred is methylene-bis-acrylamide ("MBA") which is employed in the examples herein as a 1% solution in water.

A particular aspect of the invention is the criticality of the humectant component when hydrophobic drugs are employed. Polyols such as glycerol (which has been the preferred humectant in the prior art polymeric drug dispersion matrix formulations) produce unacceptable cured products in which the drug has little or no solubility in the cured matrix. In the products of the invention the drug does not separate out into noticeably discrete particles although some opacity may be encountered. In the preferred embodiments the gels are clear or only slightly cloudy.

The drugs used in the inventive formulations must have substantial solubility, i.e. at least about 60% dissolved, in the humectant in both the monomer formulations and the polymer matrix. This property is important to maintaining consistent polymer properties and in assuming that the drug can be

reliably delivered to the patient's skin. Preferably the drug is at least about 80% dissolved in the humectant.

At least one drug is substantially dissolved in the polymeric gels of the invention. The type of drug which may be employed may be any drug which is capable of being transdermally or topically administered to a patent and which can be substantially dissolved in the polymerizable and polymerized formulations at effective dosage levels. A particular benefit of the invention is the ability to dissolve and deliver hydrophobic drugs in a hydrophilic adhesive hydrogel. The most preferred class of drugs useful in the invention are adrenocorticosteroids, such as hydrocortisone and its pharmaceutically acceptable esters, e.g. acetate, butyrate, valerate, and hemisuccinate esters; betamethasone and its pharmaceutically acceptable esters, e.g. adamantoate, benzoate, diproprionate, valerate and divalerate esters; fluocinoide; and triamicinolone acetonide. Other drugs including antiinfectives such as tolnaflate, analgesics such as salicylic acid and anesthetics such as lidocaine may be used. Depending on solubility and desired dosage factors, the drug may suitably be at levels of a few ppm to 20% or more based on the total weight of the polymerizable composition. Typical levels will range from 0.05% - 15%. Suitable levels for hydrocortisone range up to about 1%, whereas the hemisuccinate may be employed at levels of 2.5% or more by weight.

While the invention provides unique compatibility advantages when the drug is a hydrophobic drug, it is not necessary that the drug be a hydrophobic drug to practice the invention. For instance, water soluble antibiotics and other antiinfective agents are also suitably used in the drug delivery gels of the invention. Examples of such antiinfective agents include erythromycin, neomycin sulfate, gentamicin or its sulfate, sodium cephalothin, polyvinylpyrrolidone-iodine complex and the like.

The compositions of the invention may also employ other ingredients such as thickeners colorants, reinforcing agents, etc., which do not materially detract from the performance of the cured polymeric gels for their intended purposes.

As previously mentioned, curing of the composition may be accomplished by conventional techniques. For instance, the polymerization procedures of Examples 1-9 of US 4,391,278 may be readily adapted by those skilled in the art for use with formulations as claimed herein to produce acceptable polymer gel products. However, it is most preferred that the compositions be photocured. For photocuring an effective amount of a conventional photoinitiator is employed. Suitably the photoinitiator is added at a level of between about 75ppm and 1500ppm. Conveniently the photoinitiator may be added as a solution in a compatible solvent such as isopropanol.

Suitable photoinitiator compounds include benzoin, benzophenone, and acetophenone derivatives such as dimethoxyacetophenone or diethoxyacetophenone, and (1-hydroxy)cyclohexyl phenyl ketone sold under the tradename Irgacure™ 184.

The invention is illustrated by the following non-limiting examples.

Example 1

A gel material of the invention was prepared by combining (where parts are by weight) 45.25 parts of a 58% solution of NaAMPS in water, 8 parts of a 1% N,N-methylene-bis-acrylamide solution in deionized water and a drug/humectant premix (comprising 39.60 parts polyethylene glycol M.W. = 300 (PEG 300) and 0.99 parts hydrocortisone stirred together for 30 minutes) in a mixing tank and stirring for one hr. at 100 rpm. Silica, 2.48 parts, was added and stirred for an additional 30 min. Acrylic acid, 2.77 parts, was then added and the mixture stirred an additional 20 min. A photoinitiator, Irgacure™ 184 was then added (1 part of a 3% solution in isopropanol) and the mixture stirred for 10 min. longer. The mixture was degassed under vacuum, coated through a mesh reinforcement layer of spun bonded polyester (Reemay 2055) onto a polyester sheet material (5 mil Mylar™). The coating/reinforcing fabric layer was 0.15" thick. The composition was then cured with UV irradiation of 1.77 mW/cm^2 from a 365 nm Hg vapor lamp for 1.5 minutes. The cured gel was covered with a polyurethane top liner (2.5 mil Bertek™ Medifilm U426) to give a laminate which could be cut into desired shapes. The bottom polyester layer is readily peeled

off to expose the gel surface which is slightly to moderately tacky and leaves no noticeable residue when placed on skin and then removed. The gel has sufficient adhesion to remain on skin for at least 8 hours.

Example 2

A blank patch material prepared as in Example 1, except that no drug was incorporated therein, was used as a test receptor material to evaluate bioavailabity of the hydrocortisone in the products of the invention and in commercial hydrocortisone ointments.

A blank gel patch was covered with a thin polycarbonate membrane through which the drug had been demonstrated to pass freely. Test patches similarly prepared except that they contained 0.5% and 1.0% hydrocortisone were applied to the top side of the polycarbonate membrane and maintained at 37°C. Contact times of 1 hr, 2 hrs, 4 hrs, 6 hrs, 8 hrs and 24 hrs were obtained after which the Blank patch was separated from the membrane, and extracted with methanol. The amount of hydrocortisone which had migrated from the test patch to the Blank patch was determined on the extract. Comparative measurements were made using commercial hydrocortisone ointments applied to the top side of the polycarbonate membrane. Results are shown in Fig. 1 where the various formulations tested are represented as follows.

TABLE I

Test Patch	
1	1% hydrocortisone
2	0.5% hydrocortisone
Comparative Ointments	
A	Cortril™ 1% hydrocortisone
B	Fougera Cream 1% hydrocortisone
C	Fougera Ointment 1% hydrocortisone
D	NutraCream 1% hydrocortisone
E	Hytone Ointment 1% hydrocortisone

Figure 1 demonstrates that hydrocortisone migrated as easily from both the 0.5% and 1.0% test patches of the invention as it did from the most mobile ointment formulations (1% Cortril™).

Example 3

Formulations were prepared having the following ingredients:

TABLE II

Ingredient	% By Weight
58% NaAMPS soln.	45.7
1% MBA Solution	8.0
Acrylic Acid	2.8
Silica	2.5
Hydrocortisone	1.0
Humectant	40.0

Different humectants were used as shown in Table III. The formulations were observed for suitable solubility in the monomer formulation and those showing reasonable compatibility of the drug were cured by adding 1% by weight of a 3% solution in isopropanol of (1-hydroxy)cyclohexyl phenyl ketone (Irgacure™ 184) and irradiating as in Example 1. The results shown in the Table III demonstrate the criticality of the selection of humectant.

TABLE III

Formulations	Humectant	Observation
3	PEG 200	Acceptable gel, slightly opaque. Hydrocortisone mostly dissolved.
4	PEG 400	Slightly opaque. Hydrocortisone mostly dissolved.
5	PEG 600	Good gel. Hydrocortisone nearly all dissolved
6	glycerol	Unacceptable. Dissolution of hydrocortisone particles was not apparent in uncured formulation. Curing was attempted but hydrocortisone particles were observed in the cured gel as well.
7	propylene glycol	Good product. Hydrocortisone totally dissolved in uncured formulation. Cured gel was clear and somewhat softer than PEG based gels.
8	dipropylene glycol	Good product. Hydrocortisone totally dissolved in uncured formulation. Cured gel was clear and somewhat softer than PEG based gels.
Comparative Formulations		
F	Sorbitol	Unacceptable. No dissolution of hydrocortisone in the uncured formulation.
G	Polyol-P	Unacceptable. No dissolution of hydrocortisone in the uncured formulation.
H	2-methyl-2,4-pentanediol	Unacceptable. Hydrocortisone totally dissolved in uncured formulation but phase separated on polymerization giving opaque non-tacky material.
I	PPG 425	Unacceptable. Clear uncured solution but drug came out of solution when cured. Gel is opaque and tack free. Syneresis of the humectant occurred.
J	PPG 725	Unacceptable. The uncured formulation was opaque and too thick to work with.
K	Polyglycol P-2000	Unacceptable. A very thick opaque white formulation. Abandoned without curing.
L	Polyglycol 15-200	Unacceptable. Clear solution uncured but an opaque tack-free clear cured product in which the drug appeared to have come out of solution.
M	Pluronic L10	Unacceptable. Opaque tack-free cured product.
N	Pluronic L35	Unacceptable. Opaque tack-free cured product.
O	Pluronic L64	Unacceptable. Uncured formulation was too thick to stir. Abandoned without curing.

Example 4

Formulations were prepared as shown in Table IV. In all cases acceptable moderately adhesive gels were obtained upon photocuring after adding 0.5% - 1.0% of a 3% Irgacure™ 184 solution.

TABLE IV

Ingredient	9	10	11	12	13	14	15*	16	17
NaAMPS	49.7	50.2	41	48.6	47.7	47.7	46.2	46.65	46.6
1% MBA	4.0	4.0	4	6.0	6.0	6.0	6.0	8.0	8.0
Silica	2.5	2.5	-	2.5	2.5	2.5	2.5	2.5	2.5
PEG 300	40.0	40.0	35	40.0	40.0	30.0	40.0	40.0	40.0
Acrylic Acid	2.8	2.8	5	2.8	2.8	2.8	2.8	2.8	2.8
Lidocaine	1.0	0.5	-	-	-	-	-	-	-
Salicyclic Acid	-	-	15	-	-	10.0	-	-	-
Hydrocortisone Hemisuccinate	-	-	-	-	-	-	2.5	-	-
Tolnaflate	-	-	-	-	1.0	1.0	-	-	-
Betamethazone Valerate	-	-	-	0.10	-	-	-	-	-
Fluocinonide	-	-	-	-	-	-	-	0.05	-
Triamcinolone Acetonide	-	-	-	-	-	-	-	-	0.10

* Neutralized to pH 7.38 with 50% NaOH before polymerization.

WHAT IS CLAIMED IS:

1.) A polymerizable composition comprising:

20%-50% of a monofunctional monomer component, at least 75% of said component comprising 2-acrylamido-2-methylpropane sulfonic acid or a salt thereof, the balance being selected from the group consisting of acrylic acid, water soluble acrylic functional monomers and vinyl pyrrollidone;

30%-50% of a glycol component selected from the group consisting of compounds of the formula

$$HO\text{-}(C_2H_4O)_n\text{-}H,$$

$$HO\text{-}(C_3H_6O)_m\text{-}H$$

and mixtures thereof, where n is in the range of about 4 to about 16 and m is 1-4;

between about 0.02% and about 0.20% of a crosslinking monomer;

an amount of a free radical polymerization initiator effective for initiating polymerization of said monofunctional monomer and crosslinking monomer components; and

a therapeutically effective amount of a topically or transdermally deliverable drug, at least about 60% of said drug being dissolved in the formulation.

2.) A composition as in claim 1 wherein said drug is a hydrophobic drug.

3.) A composition as in claim 2 wherein the hydrophobic drug is a corticosteroid.

4.) A composition as in claim 3 wherein the hydrophobic drug is selected from the group consisting of hydrocortisone and its pharmaceutically acceptable esters, betamethasone and its pharmaceutically acceptable esters, fluocinoide and triamcinolone acetonide.

5.) A composition as in claim 4 wherein the hydrophobic drug is hydrocortisone.

6.) A composition as in claim 5 wherein the hydrocortisone is present at a level of about 0.5-1% by weight.

7.) A composition as in claim 3 wherein the hydrophobic drug is hydrocortisone hemisuccinate.

8.) A composition as in claim 7 wherein the hydrocortisone hemisuccinate is present at a level of about 0.5-3.0% by weight.

9.) A composition as in claim 7 having a neutral pH.

10.) A composition as in claim 1 wherein the drug is an analgesic, antiinfective or anesthetic.

11.) A composition as in claim 1 wherein the monofunctional monomer component is present at a level of between about 25% and about 50%.

12.) A composition as in claim 11 wherein the monofunctional monomer component includes acrylic acid in addition to said 2-acrylamido-2-methylpropane sulfonic acid or salt thereof.

13.) A composition as in claim 12 wherein the acrylic acid comprises between about 6% and about 18% of said monofunctional monomer component.

14.) A composition as in claim 1 wherein the humectant is polyethylene glycol 300.

15.) A tacky, drug containing adhesive leaving substantially no residue when pulled from skin comprising a cured product of the formulation of claim 1.

16.) An adhesive as in claim 15 wherein the drug is substantially dissolved in said cured formulation.

17.) An adhesive as in claim 15 wherein the drug is a corticosteroid, antiinfective, analgesic or anesthetic.

18.) An adhesive as in claim 17 wherein the drug is selected from hydrocortisone and its pharmaceutically acceptable esters, betamethasone and its pharmaceutically acceptable esters, fluocinoide and triaminicinolone acetonide.

19.) An adhesive as in claim 18 wherein the drug is hydrocortisone or an ester thereof.

20.) An adhesive as in claim 15 wherein the drug is a hydrophobic drug.

21.) A therapeutic patch for topical or transdermal application of a drug having a laminate structure comprising a flexible top liner, a reinforced layer of an adhesive as in claim 15 and a peelable bottom release liner.

22.) A patch as in claim 21 wherein the flexible top liner is a flexible polyether polyurethane sheet material, the adhesive is reinforced with a fabric material and the bottom release liner is a polyester sheet material.

23.) A patch as in claim 22 wherein the reinforcing fabric is a spun bonded polyester fabric.

24.) A patch as in claim 21 prepared by applying a polymerizable composition as in claim 1 to said bottom liner through said reinforcing fabric, photocuring the polymerizable composition and then covering the composition with the bottom liner.

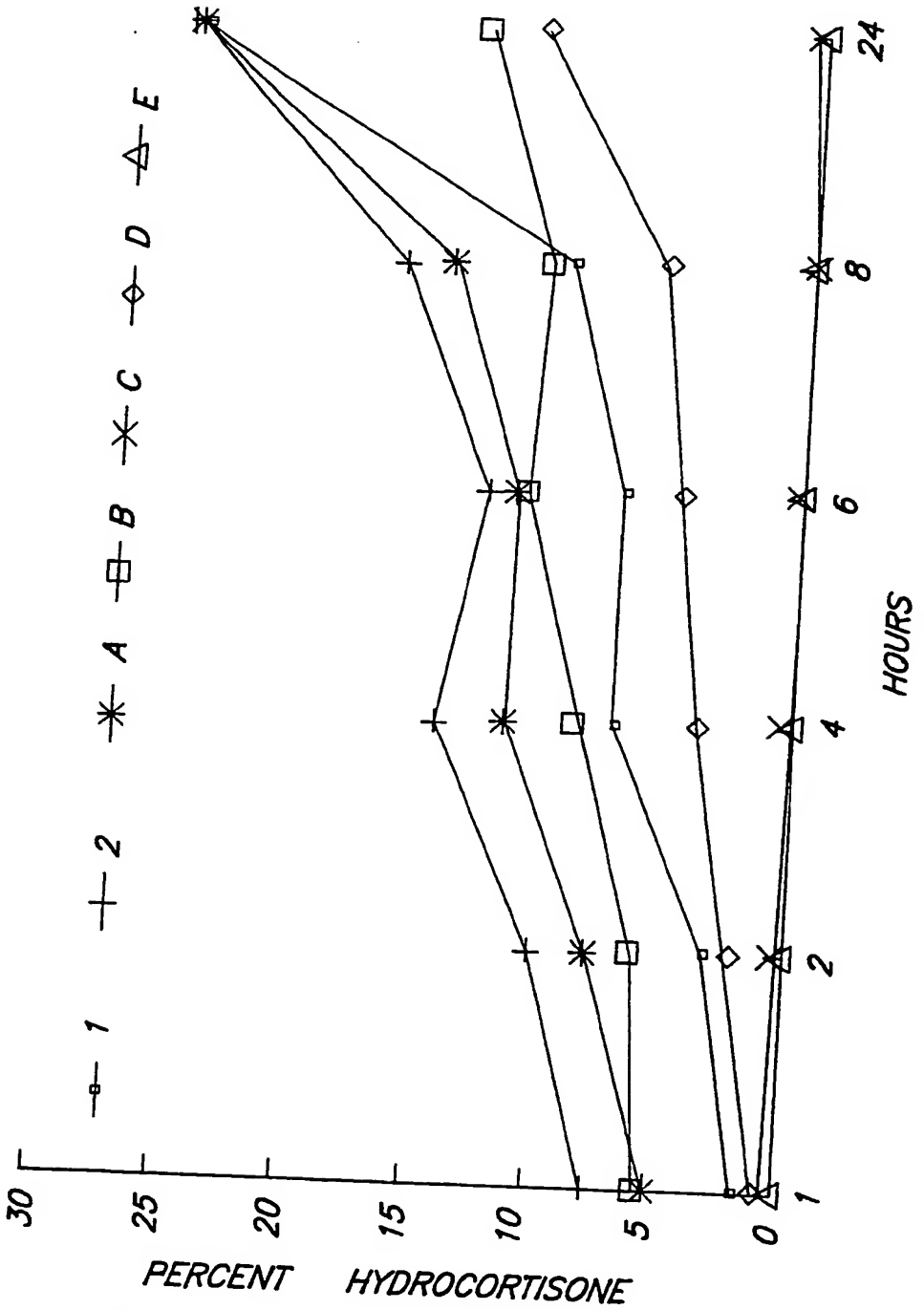

FIG. 1

SUBSTITUTE SHEET

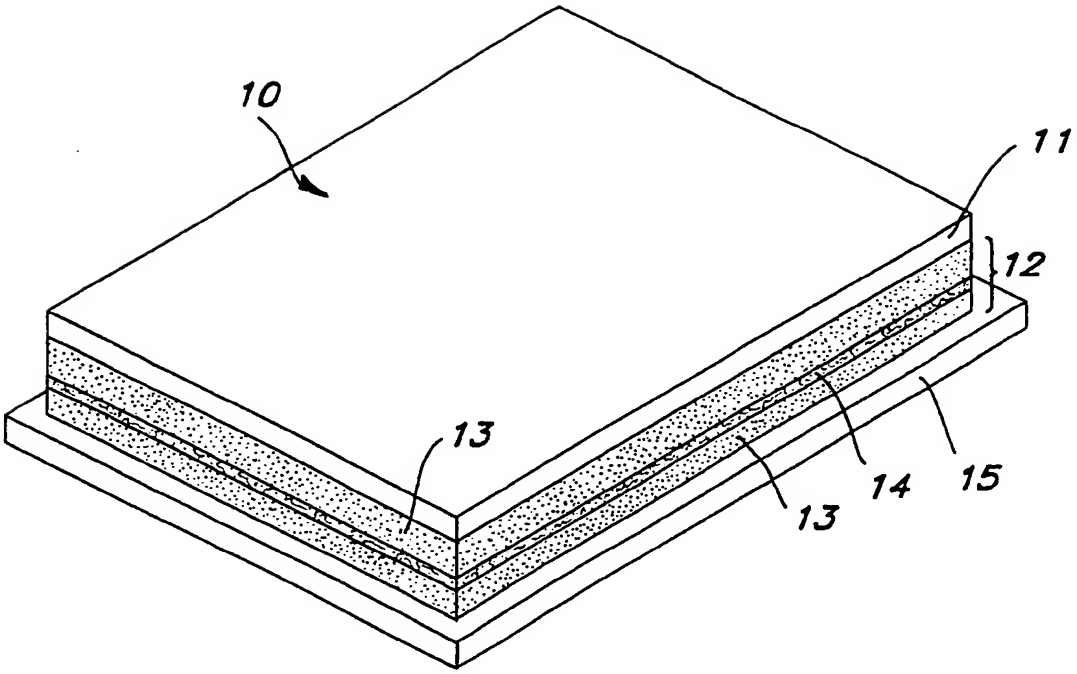

FIG. 2

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/04130

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61L15/16

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61L ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	US,A,3 931 087 (J.C. BAATZ & A.E. COREY) January 6, 1976 see abstract ---	1-24
A	US,A,3 929 741 (R.A. LASKEY) December 30, 1975 see abstract ---	1-24
A	US,A,3 632 740 (R.C.V. ROBINSON ET AL.) January 4, 1972 cited in the application see abstract ---	1-24

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
02 OCTOBER 1991	16 OCT 1991
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	LEHERTE C.F.M.

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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

US 9104130
SA 48508

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
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02/10/91

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US-A-3632740	04-01-72	None		

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dimethacrylate, alkoxylated triacrylate, polyethylene glycol diacrylate (PEG400 or PEG600), methylene bis acrylamide.

The aqueous reactive mixture optionally further comprises a surfactant, an additional monomer, an electrolyte, a processing aid (which is preferably a hydrophobic polymer), a water soluble polymer suitable for forming an interpenetrating polymer network, a non-hydrophilic polymer, an antimicrobial agent (e.g. citric acid, stannous chloride) and/or, for drug delivery applications, pharmaceutically active agents, the latter being designed to be delivered either passively (e.g. transdermally) or actively (e.g. iontophoretically) through the skin.

The process used to prepare bioadhesive compositions in accordance with the invention comprises mixing the ingredients to provide a reaction mixture in the form of an initial pre-gel aqueous based liquid formulation, which is then converted into a gel by a free radical polymerisation reaction. This may be achieved for example using conventional thermal initiators and/or photoinitiators or by ionizing radiation. Photoinitiation is a preferred method and will usually be applied by subjecting the pre-gel reaction mixture containing an appropriate photoinitiation agent to UV light after it has been spread or coated as a layer an siliconised release paper or other solid substrate. The processing will generally be carried out in a controlled manner involving a precise predetermined sequence of mixing and thermal treatment or history. One preferred feature of the process according to the invention is that no water is removed from the hydrogel after manufacture.

Additional Monomer

The composition according to the invention preferably comprises one or more additional monomers. A suitable additional monomer is an ionic monomer, preferably a cationic monomer. Additional monomers, when present, are preferably included in an amount of up to 10% by weight.

A preferred cationic monomer is a quaternary ammonium salt. An especially preferred cationic monomer is (3-acrylamidopropyl)trimethyl ammonium chloride or [2-(acryloyloxy)ethyl]trimethyl ammonium chloride.

Plasticiser

The compositions according to the invention generally comprise, in addition to a crosslinked polymeric network, an aqueous plasticising medium. Plasticisers are generally used in the invention to control adhesive properties.

The aqueous plasticising medium optionally additionally comprises a polymeric or non-polymeric polyhydric alcohol (such as glycerol), an ester derived therefrom and/or a polymeric alcohol (such as polyethylene oxide). Glycerol is the preferred plasticiser. An alternative preferred plasticiser is an ester derived from boric acid and a polyhydric alcohol (such as glycerol). The aqueous reactive mixture preferably comprises from 10% to 50%, preferably from 10% to 45%, of plasticiser (other than water) by weight of the mixture.

One advantage of this invention is that it provides hydrogel dressings that are adhesive to dry skin which have water activities from 0.4 to 0.85, preferably from 0.65 to 0.8 and more preferably from 0.7 to 0.8. The latter materials have a greater tendency to wet (i.e. donate water to the skin) rather than to extract. These materials do not encourage the growth of microbial agents and they can be sterilised. Hydrogels based on the curing of ionic monomers are preferred as they enable a greater control of the activity of water. For materials with requirements for higher water activities, e.g. from 0.75 to 0.85, monomers which are potassium salts are preferred, e.g. SPA, K AMPS, and K acrylate.

The water activity of the bioadhesive composition is ideally selected to suit the wound to which the dressing is to be applied. Thus different compositions may be provided for application to different kinds of wounds

such as burns and cuts. The water activity, and thus absorption characteristics, of the composition are optimised to prevent drying of the wound or to absorb excess exudate from the wound.

Interpenetrants

The compositions preferably additionally comprise a water soluble polymer suitable for forming an interpenetrating polymer network. Hydrogels based on interpenetrating polymer networks (IPN) are well known. An IPN has been defined as a combination of two polymers, each in network form, at least one of which has been synthesised and/or crosslinked in the presence of the other. As will be appreciated, this combination will generally be a physical combination rather than a chemical combination of the two polymers. IPN systems may be described by way of example as follows:

> Monomer 1 is polymerised and crosslinked to give a polymer which is then swollen with monomer 2 plus its own crosslinker and initiator.

If only one polymer in the system is crosslinked the network formed is called a semi-IPN. Although they are also known as IPN's, it is only if there is total mutual solubility that full interpenetration occurs. In most IPN's there is, therefore, some phase separation but this may be reduced by chain entanglement between the polymers. It has also been reported that semi IPN's can be made in the presence of carrier solvents (for example water in the case of hydrophilic components).

It has been found that polymerising and crosslinking water soluble monomers in the presence of water soluble polymers, water and polyhydric alcohols produces hydrogel materials with enhanced rheological and consequently adhesive properties.

Suitable water soluble polymers for the formation of semi IPN's include poly (2-acrylamido-2-methylpropanesulphonic acid) or one of its salts

and its copolymers, poly (acrylic acid-(3-sulphopropyl) ester potassium salt), copolymers of NaAMPS and SPA, polyacrylic acid, polymethacrylic acid, polyethylene oxide, polyvinyl methyl ether, polyvinyl alcohol, polyvinyl-pyrrolidone, its copolymers with vinyl acetate, dimethylaminoethyl methacrylate, terpolymers with dimethylaminoethyl methacrylate and vinyl-caprolactam, polysaccharides such as gum arabic, karaya gum, xanthan gum, guar gum, carboxymethyl cellulose (CMC), NaCMC, hydroxypropylmethyl cellulose (HPMC), hydroxyethyl cellulose (HEC) or combinations thereof.

The amount of interpenetrant polymer used will be dependent on the mechanical and rheological properties required as well on consideration of processing conditions. If the interpenetrant polymer used increases the viscosity of the pre-gel mix beyond 5000 centipoise it has been found that the monomers do not polymerise and crosslink on an acceptable time scale (should be less than 60 seconds, preferably less than 10 seconds). The viscosity depends on the nature and molecular weight of the interpenetrant and the nature of pre-gel processing.

Of the natural polysaccharides, gum arabic or maltodextrin is usually preferred due to its cold water solubility and lesser effect on viscosity compared with, for example, karaya gum. A higher concentration of gum arabic than karaya may therefore be used if desired, enabling a wider control of hydrogel properties. It has also been found that the processing steps for assembling the pre-gel formulation can be critical with respect to the properties of the manufactured hydrogel. For a given formulation, if the components are assembled at 25°C and cured different adhesive properties are obtained compared to those that have been heated to 70°C. Solutions containing natural polysaccharides become less opaque indicative of improved solubility. The activity of water in compositions prepared from heat treated pre-gels generally is lower than in non heat treated pre-gels.

Other additives

The composition preferably comprises a hydrophobic polymer. Hydrophobic polymers may be incorporated either in the presence or absence of interpenetrant polymers to form phase separated materials. The preparation of two phase composites consisting of a hydrophilic polymer containing an ionically conducting continuous phase and domains of a hydrophobic pressure sensitive adhesive which enhance adhesion to mammalian skin have been reported in U.S. Patent 5338490. The method of preparation described therein involved casting a mixture (as a solution and or suspension) consisting of the hydrophilic polymer containing phase and hydrophobic components onto a substrate and then removing the solvent. It has been found, however, that adhesive ionically conducting hydrogels may be better prepared by combining the hydrophobic polymer (preferably as an emulsion) with the components of the pre-gel reaction mixture and casting these onto a substrate and curing. In other words, there is no need to remove a solvent in order to form useful materials. Furthermore, the hydrophilic phase of the composition in addition to being a crosslinked network may also be an IPN or semi IPN.

It is believed that when hydrophobic polymers are incorporated in this way that the hydrophobic component segregates to the surface (as determined by Fourier transform infrared attenuated total reflectance spectroscopy, FTIR ATR, approximate sampling depth 1 μm using a ZnSe crystal or 0.25μm with a Germanium crystal) and that it is the amount of the hydrophobic component present in the surface that influences the adhesion to a wide variety of materials. The greater the amount of the hydrophobic component in the surface the greater the adhesion. In U.S. Patent 5338490 weight ratios of the hydrophilic phase to the hydrophobic phase of 60:1 to 8:1 were claimed. In hydrogel adhesives of between 100 to 2000 microns thick made in accordance with the present invention, ratios of hydrophilic to hydrophobic components

ranging from 7:1 to 1:20 have been found to be preferable, especially when these ratios are present in the surface of the adhesive composition. In the process of the present invention, however, it may take up to 72 hours from the initial curing of the adhesive hydrogel for the segregation of the hydrophobic materials to the surface, as defined by the ATR sampling depth, to be complete.

Preferably, the hydrophobic pressure sensitive adhesive in such embodiments is selected from the group consisting of polyacrylates, polyolefins, silicone adhesives, natural or synthetically derived rubber base and polyvinyl ethers or blends thereof. Preferably the hydrophobic pressure sensitive adhesive in these embodiments is an ethylene/vinyl acetate copolymer such as that designated DM137 available from Harlow Chemicals or vinyl acetate dioctyl maleate such as that designated Flexbond 150 and sold by Air Products. Those skilled in the art will also know that the molecular weight and comonomer ratios may be altered to control the properties of hydrophobic pressure sensitive adhesives. In general, the degree of surface segregation exhibited by such hydrophobic pressure sensitive adhesive (HPSA) will be dependent on factors such as composition of the HPSA, viscosity of the pre-gel mixture, temperature and rate of curing.

The bioadhesive composition according to the invention preferably is such that the relative amount of hydrophobic polymer (which is the amount of hydrophobic polymer relative to the amount of monomer) is preferably at least four times greater, more preferably at least eight times greater, at the surface of the composition compared to what it is in the bulk of the composition. The relative amount at the surface is preferably the relative amount in the composition at a depth of up to 1 micron (as measured using FTIR ATR using a ZnSe crystal), preferably up to 0.25 micron (as measured using FTIR ATR using a Germanium crystal). The relative amount is measured by obtaining the ratio of the peak height of the peak in the carbonyl region for the hydrophobic

polymer to the peak height of the peak in the carbonyl region for the first monomer, using the relevant FTIR ATR technique. The wave number values for the relevant peaks for the hydrophobic polymer and the monomer are well known.

More preferably, the ratio of the relative amount in the surface of the composition at a depth of up 0.25 micron to the relative amount in the surface of the composition at a depth of up 1 micron is more than 1:1, more preferably more than 1.25:1, most preferably more than 1.5:1.

Surfactant

The composition according to the invention optionally includes a surfactant.

Any compatible surfactant may be used. Nonionic, anionic and cationic surfactants are preferred, either alone or in combination. The surfactant is preferably included in an amount from 0.1% to 20% by weight, more preferably 0.1% to 10% by weight.

Carrier Material

The carrier material used in the wound dressings according to the invention is preferably perforated. Generally any conventional carrier material known for use in dressings can be used as the carrier material. It is preferable that the carrier material is made from inelastic fibres, preferably continuous inelastic fibres. The carrier material is generally either knitted, extruded, woven or non-woven. It is optionally in the form of, for example, a foam or a film. The smallest dimension of each perforation in the carrier material is preferably from 0.5 to 5.0mm, more preferably from 1.0 to 3.0mm. The fibres are made from cotton, rayon, polyester, polyamide, polypropylene, polyamide or wool or a mixture thereof.

Preparation of Wound Dressing

There are a variety of possible ways in which the process of the invention may be carried out.

Examples of ways in which process (a) may be performed include extruding the aqueous reaction mixture onto a web which, in the case of an automated process, is preferably moving. The web is preferably made from paper, polyester, polyolefin or any other material commonly used in the art. The carrier material is either laid on top of the aqueous reaction mixture after it has been extruded or is laid on top of the web and the aqueous reaction mixture is extruded over it. The assembly is then cured. Where the carrier material is perforated, it may be necessary to blow air through the assembly before curing to ensure that the perforations are free from the bioadhesive composition.

An alternative way in which process (a) according to the invention may be carried out is by coating the carrier material with the aqueous reaction mixture by, for example, dipping the carrier material in a bath of the aqueous reaction mixture and then passing the coated carrier material over or round a single roller or through a nip roller. The assembly is then cured. Again, if the carrier material is perforated, it may be necessary to blow air through the assembly before curing to ensure that the perforations are free from the bioadhesive composition.

Process (b) according to the invention may be performed, for example, by laminating a sheet of the bioadhesive composition with the carrier material. The sheet of bioadhesive composition is preferably supported by a plastic or coated material to act as a protective release sheet.

In both processes according to the invention, the aqueous reaction mixture is preferably coated in an amount of from 0.1 to 2 kg/m^2.

The wound dressing according to the invention is optionally coated on

one or both sides with at least one release sheet. The release sheets are generally either made of plastic or coated paper e.g. siliconised paper.

The invention will be further described with reference to FIGURES 1 to 5 of the accompanying drawings and the following Examples in connection with bioadhesive compositions suitable for use in wound dressings.

EXAMPLE 1

In 20 parts of polyethylene glycol diacrylate (pEG600) (product of UCB Chemicals marketed under the trade name designation of Ebacryl 11) were dissolved 6 parts of 1-hydroxycyclohexyl phenyl ketone (product of Ciba and marketed under the trade name designation of Irgacure 184). The solution so produced is herein designated solution A (XL/PI). Separately, 50 parts of the potassium salt of 3-sulphopropyl acrylate (SPA) (product of Raschig) were dissolved in 50 parts water to form solution B. A further solution designated solution C consisted of 50 parts water, 50 parts of the sodium salt of 2-acrylamido-2-methylpropane sulphonic acid (NaAMPS) product of the Lubrizol Corporation and marketed as a 50% aqueous solution under the trade name LZ2405). Mixtures of solutions B and C in the ratios of 100:0, 90:10, 60:40, 50:50, 40:60, 10:90 and 0:100 were made to form pre-gel solutions. To 80 parts of each of these pre-gel solutions, 0.15 parts of solution A, 5 parts potassium chloride and 20 parts distilled water were added. The pre-gel solutions were coated onto siliconised release paper at a coat weight of 0.8 kilograms per square meter and exposed to ultraviolet radiation by being passed under a medium pressure mercury arc lamp at a speed of 5 meters per minute to form clear self supporting gels. The residence time under the lamp was 4 seconds. The storage moduli(G') of 20mm diameter discs stamped from the gels were recorded on a Rheometric Scientific RS-5 rheometer at 37°C. The G' values at 1rad are recorded in Table 1. With the exception of the gels containing 90 and 100 parts SPA, the gels produced had acceptable tack and

peel properties on the skin. From the data in Table 1 relatively linear changes in storage modulus are obtained on increasing or decreasing the SPA to NaAMPS ratio.

The gels were found to lose adhesion on water uptake and are thus suitable for use in wound dressings.

In the above Example, and in the following Examples wherever parts are mentioned they are meant as parts by weight unless otherwise specified.

TABLE 1

NaAMPS SolutionC	80	72	48	40	32	8	0
SPA SolutionB	0	8	32	40	48	72	80
Distilled Water	20	20	20	20	20	20	20
XL/PI SolutionA	0.15	0.15	0.15	0.15	0.15	0.15	0.15
KCl	5	5	5	5	5	5	5
G'(Pa) @ 1rad/s	4,198	3,389	2,471	2,205	1,759	703	492

EXAMPLE 2

In 20 parts of polyethylene glycol diacrylate (pEG600) (product of UCB Chemicals marketed under the trade name designation of Ebacryl 11) 6 parts of 1-hydroxycyclohexyl phenyl ketone (product of Ciba and marketed under the trade name designation of Irgacure 184) were dissolved. (This solution is designated solution A) (XL/PI). Separately 58 parts of the potassium salt of 3-sulphoproylacrylate (SPA) (product of Raschig) were dissolved in 58 parts distilled water to form solution D. A further solution designated solution E consisted of 42 parts water, 58 parts of the sodium salt of 2-acrylamido-2-methylpropane sulphonic acid (NaAMPS) (a product of the Lubrizol Corporation marketed as a 58% aqueous solution under the trade name

LZ2405A). Mixtures of solutions D and E in the ratios 100:0, 90:10, 60:40, 50:50, 40:60, 10:90 and 0:100 were made to form pre-gel solutions. To 100 parts of each of these pre-gel solutions, 0.17 parts of solution A and 3 parts potassium chloride were added. The pre-gel solutions were coated onto siliconised release paper at a coat weight of 0.8 kilograms per square meter and passed under a medium pressure mercury arc lamp at a speed of 5 meters per minute to form clear self-supporting gels. Storage moduli were measured as in Example 1 and are recorded in Table 2. As in the gels described in Example 1 the changes in the elastic or storage modulus G'(Pa) are linear with respect to the increasing or decreasing ratio of NaAMPS to SPA. All the gels produced possess acceptable tack and peel strength against skin. The gels with NaAMPS:SPA ratios in the range of 60:40 to 40:60, however, have a better balance of reusability and peel strength.

The gels were found to lose adhesion on water uptake and are thus suitable for use in wound dressings.

TABLE 2

NaAMPS SolutionE	100	90	60	50	40	10	0
SPA SolutionD	0	10	40	50	60	90	100
XL/PI SolutionA	0.17	0.17	0.17	0.17	0.17	0.17	0.17
KCl	3	3	3	3	3	3	3
G'(Pa) @ 1 rad/s	15,142	14,333	11,073	10,672	9,920	6,280	5,199

Upon varying the amount of the cross-linking agent a substantially linear change in the elastic modulus G' can also be obtained, as illustrated by the graph of FIGURE 1.

EXAMPLE 3

To 57 parts of a 58% solution of the sodium salt of 2-acrylamido-2-methylpropane sulphonic acid (NaAMPS) (LZ2405A) 10 parts of a 58% solution of the potassium salt of 3-sulphopropyl acrylate (SPA) were added along with 5 parts potassium chloride and stirred until the potassium chloride has dissolved. This solution was then mixed with 30 parts glycerol for 30 minutes. To the latter solution were added 0.15 parts of a solution containing 20 parts of polyethylene glycol diacrylate (pEG600) (product of UCB Chemicals marketed under the trade name designation of Ebacryl 11) in which 6 parts of 1-hydroxycyclohexyl phenyl ketone (product of Ciba and marketed under the trade name designation of Irgacure 184) were dissolved. The so-formed pre-gel solution was then cured as in Example 1. The gels were found to lose adhesion on water uptake and are thus suitable for use in wound dressings. Good skin adhesion properties were obtained for this gel.

EXAMPLE 4

The method of Example 3 was repeated with 1 part citric acid being added with the potassium chloride. The adhesion to skin and reusability characteristics for this gel of Example 4 containing citric acid and SPA were better than the gel described in Example 3.

EXAMPLE 5

The formulations listed in Table 4 were prepared using the following method which is for formulation 5a. To 58 parts of a 50% aqueous solution of the sodium salt of 2-acrylamido-2-methylpropane sulphonic acid (NaAMPS) (LZ2405) 2 parts of the potassium salt of 3-sulphopropyl acrylate (SPA) were added along with 1.575 parts of acrylic acid and stirred. This solution was then mixed with 37 parts glycerol for 30 minutes. To the latter solution were added 0.175 parts of solution (F). Solution F contains 20 parts of an alkoxylated

triacrylate (product of UCB Chemicals marketed under the trade name designation of IRR 210) in which 1.4 parts of 1-hydroxycyclohexyl phenyl ketone (product of Ciba and marketed under the trade name designation of Irgacure 184) are dissolved. The so-formed pre-gel solution was then cured as in Example 1. The G' and G" moduli were measured from 20mm diameter discs of the gel using a Rheometric Scientific RS-5 rheometer at 37°C.

To prepare formulation 5b, the same method was repeated except that 0.15 parts of solution F were used instead of 0.175 parts.

To prepare formulations 5c and 5d, the same method used for formulation 5a was repeated except that the parts by weight were changed to the figures given in Table 4A. The potassium chloride was added instead of the acrylic acid; for formulation 5d, deionised water was also added.

TABLE 4

Composition in parts by weight				
Formulation	5a	5b	5c	5d
50% NaAMPS	58	58	75	75
KCl			5	5
Acrylic Acid	1.575	1.575		
SPA	2	2	2	2
Glycerol	37	37	25	25
DI WATER				3
PI/XL (Solution)	0.175 (F)	0.15 (F)	0.15 (A)	0.15 (A)
G'(Pa) @ 1 rad/s	1455		1054	
G'(Pa) @ 100 rad/s	5174		4613	
G'' (Pa) @ 1 rad/s	601		488	
G'' (Pa) @ 100 rad/s	2906		2640	

EXAMPLE 6

The formulations listed in Table 5 were prepared using the following method which is for formulation 6a. To 67 parts of a 58% aqueous solution of

the sodium salt of 2-acrylamido-2-methylpropane sulphonic acid (NaAMPS) (LZ2405A) 2 parts of the potassium salt of 3-sulphopropyl acrylate (SPA) were added along with 5 parts of potassium chloride and 1 part of citric acid and stirred until the potassium chloride had dissolved. This solution was then mixed with 30 parts glycerol for 30 minutes. To the latter solution were added 0.13 parts of solution A prepared as described in Example 1. The so-formed pre-gel solution was then cured as in Example 1. The G' and G" moduli were measured from 20mm diameter discs of the gel using a Rheometric Scientific RS-5 rheometer at 37°C.

To prepare formulation 6b, the same method was repeated except that the potassium chloride and citric acid were omitted, 0.06 parts by weight of solution G were used instead of solution A and the amounts of the other ingredients were changed to the amounts given in Table 5. Solution G contains 20 parts of polyethylene glycol diacrylate (molecular weight 400) (product of UCB Chemicals marketed under the trade name designation of IRR 280) in which 6 parts of 1-hydroxycyclohexyl phenyl ketone (product of Ciba and marketed under the trade name designation of Irgacure 184) are dissolved.

To prepare formulations 6c and 6d, the same method used for formulation 6a was repeated except that citric acid was omitted, 0.06 parts of solution G were used instead of solution A and the parts by weight were changed to the figures given in Table 5.

To prepare formulation 6e, the same method used for formulation 6a was repeated except that gum arabic and the ethylene/vinyl acetate copolymer designated DM137 and sold by Harlow Chemicals were added instead of citric acid and the parts by weight were changed to the figures given in Table 5.

To prepare formulation 6f, the same method used for formulation 6a was repeated except that the ethylene/vinyl acetate copolymer designated DM137 and sold by Harlow Chemicals, polyethylene glycol (molecular weight

400) and sodium nitrate were added with the citric acid and the parts by weight were changed to the figures given in Table 5.

TABLE 5

Composition in parts by weight						
Formulation	6a	6b	6c	6d	6e	6f
58% NaAMPS	67	57	57	57	67	50
KCl	5		5	5	5	1
Citric Acid	1					1
SPA	2	10	10	10	2	18
Glycerol	30	33	33	28	30	20
Gum Arabic					2	
DM 137					2	3
PEG 400						10
Sodium Nitrate						0.05
PI/XL (Solution)	0.13 (A)	0.06 (G)	0.06 (G)	0.075 (G)	0.25 (A)	0.175 (A)
G' (Pa) @ 1 rad/s	2973	4326		3019	4637	
G' (Pa) @ 100 rad/s	9800	13986		9763	8789	
G'' (Pa) @ 1 rad/s	1265	1914		1200	1029	
G'' (Pa) @ 100 rad/s	4597	6707		4537	3952	

EXAMPLE 7

To 34.7 parts of a 58% aqueous solution of the sodium salt of 2-acrylamido-2-methylpropane sulphonic acid (NaAMPS) (LZ2405A) 34.7 parts of a 58% aqueous solution of the potassium salt of 3-sulphoproyl acrylate (SPA) were added along with 4.6 parts potassium chloride and 3 parts distilled water and stirred until the potassium chloride has dissolved. This solution was then mixed with 23.2 parts glycerol for 30 minutes. To the latter solution were added 0.15 parts of solution A prepared as described in Example 1. The so-formed pre-gel solution was then cured as in Example 1. The gels were found to lose adhesion on water uptake and are thus suitable for use in wound dressings.

EXAMPLE 8

To 20 parts glycerol, 3 parts of a hydrophobic ethylene/vinyl acetate copolymer emulsion (50% solids) (product of Harlow Chemicals marketed under the trade name DM137) and 10 parts polyethylene glycol (molecular weight 600) were added and stirred until a uniform colour was obtained. To this mixture were added 50 parts of a 58% solution of the sodium salt of 2-acrylamido-2-methylpropane sulphonic acid (NaAMPS) (LZ2405A), 16 parts potassium salt of 3-sulphopropyl acrylate (SPA) and 5 parts potassium chloride, and the solution was heated with stirring to 60°C for one hour. The mixture had changed from an opaque off white to a translucent off white appearance. The turbidity of the solutions as measured in a portable turbidity meter, product code H193703 marketed by Hanna had changed from 254ftu to 107ftu. The solution was cooled to 20°C and then there was added 0.13 parts of solution A prepared as described in Example 1. This final solution was stirred for one hour and then cured as in Example 1. The resulting gel had a G' value at 1 rad of 5328Pa. The activity of water in the gel, as determined by placing the gel into cabinets at varying levels of humidity at 40°C (40, 52, 64 and 80%RH) and measuring weight uptake or loss and extrapolating to zero weight change, was 0.62. The adhesion to skin of this gel was significantly greater than those described in the previous examples. The gels were found to lose adhesion on water uptake and are thus suitable for use in wound dressings. Analysis of the gel by attenuated total reflectance infra-red spectroscopy revealed that in the surface regions (about 1 micron or less), either the air surface or the surface in contact with the release paper, the concentration of the ethylene/vinyl acetate copolymer relative to the NaAMPS was significantly enhanced compared to the bulk composition.

EXAMPLE 9

The method of Example 8 was carried out except that with the glycerol

were added 3 parts of gum arabic. The resulting gel had a G' value at 1 rad of 5406Pa. The activity of water as determined by the method in Example 8 was 0.55. The adhesion to skin of this gel was significantly greater than those described in the previous examples. The gels were found to lose adhesion on water uptake and are thus suitable for use in wound dressings. Analysis of the gel by attenuated total reflectance infra-red spectroscopy revealed that in the surface region (about 1 micron or less), either the air surface or the surface in contact with the release paper, the concentration of the ethylene/vinyl acetate copolymer relative to the NaAMPS was significantly enhanced compared to the bulk composition.

EXAMPLE 10

The formulations shown in Tables 6 and 7 were prepared using the following method which is for formulation 10a. To 20 parts glycerol, 15 parts of a hydrophobic vinyl acetate/dioctyl maleate copolymer emulsion (product of Air Products marketed under the trade name Flexbond 150) were added and stirred until a uniform colour was obtained. To this mixture were added 44 parts of a 58% solution of the sodium salt of 2-acrylamido-2-methylpropane sulphonic acid (NaAMPS) (LZ2405A), 20 parts potassium salt of 3-sulphopropyl acrylate (SPA) and 4 parts potassium chloride, and the solution was heated with stirring to 60°C for one hour. The solution was cooled to 20°C and then there was added 0.13 parts of solution G prepared as described in Example 6. This final solution was stirred for one hour and then cured as in Example 1. The G' and G" moduli were measured from 20mm diameter discs of the gel using a Rheometric Scientific RS-5 rheometer at 37°C.

Fourier transform infrared attenuated total reflectance spectra (FTIR ATR) were taken of both the pregel mixture and of the gel formed after polymerisation using a ZnSe crystal (approximate sampling depth 1 μm). The results obtained are shown in Figures 2 and 3, respectively. The peak at around

1740 cm^{-1} corresponds to the hydrophobic polymer whereas the peak at around 1550 cm^{-1} corresponds to NaAMPS. It can be seen that before polymerisation the ratio in height of the former peak to the latter peak is about 0.25:1 whereas after polymerisation, the ratio is about 2.9:1. This shows a twelve-fold increase in the concentration of the hydrophobic polymer at the surface of the gel after polymerisation indicating that the hydrophobic polymer surface segregates. A further FTIR ATR spectrum was taken of the gel formed after polymerisation using a germanium crystal (approximate sampling depth 0.25μm). It was found that the ratio in the height of the former peak to the latter peak is 3.9:1 showing a sixteen fold increase in the concentration of the hydrophobic polymer on the surface of the gel.

To prepare formulation 10b, the same method used for formulation 10a was repeated except that a hydrophobic ethylene/vinyl acetate copolymer emulsion (50% solids) (product of Harlow Chemicals marketed under the trade name DM137) was used instead of Flexbond 150, 3 parts polyethylene glycol (molecular weight 600) were added with the hydrophobic copolymer DM137 and the parts by weight were changed to the figures given in Table 6.

FTIR ATR were taken of the gel formed after polymerisation using a ZnSe crystal (approximate sampling depth 1 μm) and a germanium crystal (approximate sampling depth 0.25μm). The results obtained are shown in Figures 4 and 5, respectively. As for formulation 10a, the peak at around 1740 cm^{-1} corresponds to the hydrophobic polymer whereas the peak at around 1550 cm^{-1} corresponds to NaAMPS. The ratio of the former peak to the latter peak for Figure 4 (the ZnSe FTIR ATR spectrum) is about 21:1 whereas the ratio for Figure 5 (the germanium FTIR ATR spectrum) is about 11:1. This again demonstrates the hydrophobic polymer segregates to the surface of the gel.

To prepare formulation 10c, the same method used for formulation 10a was repeated except that a hydrophobic ethylene/vinyl acetate copolymer

emulsion (50% solids) (product of Harlow Chemicals marketed under the trade name DM137) was used instead of Flexbond 150, 0.05 parts of sodium nitrate were added with the potassium chloride and the parts by weight were changed to the figures given in Table 6.

To prepare formulations 10d and 10e, the same method used for formulation 10b was repeated except that solution A as described in Example 1 was used instead of solution G and the parts by weight were changed to the figures given in Table 6.

To prepare formulations 10f and 10g, the same method used for formulation 10d was repeated except that potassium chloride was omitted and the parts by weight were changed to the figures given in Table 6.

TABLE 6

COMPOSITION by WEIGHT							
Formulation	10a	10b	10c	10d	10e	10f	10g
58% NaAMPS	44	44	65	35	35	35	37
KCl	4	5	5	5	5		
SPA	20	20	10	25	25	15	18
Glycerol	20	20	23	20	20	30	30
Gum Arabic							
DM 137		15	2	15	15	15	10
Flexbond 150	15						
PEG 600		3		10	10	5	5
Sodium Nitrate			0.05				
PI/XL (Solution)	0.13 (G)	0.13 (G)	0.15 (G)	0.12 (A)	0.13 (A)	0.15 (A)	0.15 (A)
G'(@ 1 rad/s)	6156	4756					
G'(@ 100 rad/s)	15219	15412					
G''(@ 1 rad/s)	1775	1840					
G''(@ 100 rad/s)	5748	7743					

To prepare formulations 10h, 10i and 10j, the same method used for formulation 10g was repeated except that the parts by weight were changed to the figures given in Table 7.

To prepare formulations 10k, 10l and 10m, the same method used for formulation 10j was repeated except that a propylene oxide/ethylene oxide block copolymer surfactant (designated PE/F127 and manufactured by BASF) was added with the glycerol and the parts by weight were changed to the figures given in Table 7.

TABLE 7

COMPOSITION by WEIGHT						
Formulation	10h	10i	10j	10k	10l	10m
58% NaAMPS	37	35	35	35	35	35
SPA	18	15	25	25	25	25
Glycerol	30	33	20	20	20	20
DM 137	10	10	15	15	15	15
PEG 600	10	5	10	10	10	10
PE/F127				1	5	9
PI/XL (Solution)	0.15 (A)	0.15 (A)	0.14 (A)	0.14 (A)	0.14 (A)	0.14 (A)

EXAMPLE 11

An aqueous reaction mixture (or so-called pregel) was prepared as described in Example 3 and coated onto a siliconised release paper at a coat weight of 0.8 kilograms per square metre. The aqueous reaction mixture was cured by passing the assembly under a medium pressure mercury arc lamp at a speed of 5 meters per minute. The residence time under the lamp was 4 seconds. The cured bioadhesive composition was then laminated by a polyurethane film (sold under the trade name SRF076 part number 93034 by Advanced Medical Solutions) to form a wound dressing.

As will be seen, the invention presents a number of different aspects and it should be understood that it embraces within its scope all novel and inventive features and aspects herein disclosed, either explicitly or implicitly and either singly or in combination with one another. Also, many detail

modifications are possible and, in particular, the scope of the invention is not to be construed as being limited by the illustrative example(s) or by the terms and expressions used herein merely in a descriptive or explanatory sense.

CLAIMS

1. A water unstable bioadhesive composition characterised in that it has:

(i) a water activity of from 0.4 to 0.9;

(ii) an elastic modulus at 1 rad/s of from 700 to 15,000 Pa;

(iii) an elastic modulus at 100 rad/s of from 2000 to 40,000 Pa;

(iv) a viscous modulus at 1 rad/s of from 400 to 14,000 Pa;

(v) a viscous modulus at 100 rad/s of from 1000 to 35,000 Pa;

wherein the viscous modulus is less than the elastic modulus in the frequency range of from 1 to 100 rad/s.

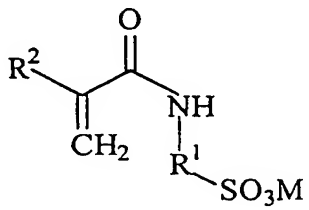
2. A bioadhesive composition according to Claim 1 which comprises an aqueous plasticiser, a copolymer of a hydrophilic unsaturated water-soluble first monomer, a hydrophilic unsaturated water-soluble second monomer together with a cross-linking agent, the first monomer having a tendency preferentially to enhance the bioadhesive properties of the composition.

3. A bioadhesive composition according to any one of the preceding claims which is obtainable by polymerising an aqueous reaction mixture comprising a hydrophilic unsaturated water-soluble first monomer, a hydrophilic unsaturated water-soluble second monomer together with a cross-linking agent, the first monomer having a tendency preferentially to enhance the bioadhesive properties of the composition.

4. A bioadhesive composition according to claim 2 or claim 3 wherein the first monomer has a tendency to enhance the mechanical strength of the composition and/or the second monomer has a tendency preferentially to increase the water activity of the composition.

5. A bioadhesive composition according to claim 4 wherein the second monomer has a tendency preferentially to lower the electrical impedance and thereby enhance the electrical conductivity of the composition.

6. A bioadhesive composition according to any one of claims 2 to 5 wherein the first monomer is a compound of formula

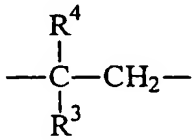


(I)

wherein R^1 is an optionally substituted hydrocarbon moiety, R^2 is hydrogen or optionally substituted methyl and ethyl, and M represents hydrogen or a cation.

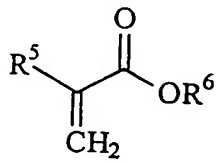
7. A bioadhesive composition according to claim 6 wherein R^1 is an optionally substituted alkyl, cycloalkyl or aromatic moiety containing from 3 to 12 carbon atoms.

8. A bioadhesive composition according to claim 6 or claim 7 wherein R1 represents



wherein R^3 represents hydrogen or an optionally substituted straight or branched chain alkyl group possessing from 1 to 6 carbon atoms and R^4 represents an optionally substituted straight or branched chain alkyl group possessing from 1 to 6 carbon atoms.

9. A bioadhesive composition according to any one of claims 2 to 8 wherein the second monomer is a compound of formula



(II)

wherein R^5 represents hydrogen or optionally substituted methyl or ethyl, R^6 represents hydrogen, a cation or R^7SO_3 wherein R^7 represents an optionally substituted alkylene moiety of 1 to 4 carbon atoms.

10. A water unstable bioadhesive composition substantially as hereinbefore described in any one of Examples 1 to 10.

11. A wound dressing which comprises a carrier material and a bioadhesive composition according to any one of the preceding claims.

12. A wound dressing according to claim 11 which coated by the bioadhesive compositions.

13. A wound dressing substantially as hereinbefore described in Example 11.

14. A process for the preparation of a wound dressing as defined in claim 11, 12 or 13 which process comprises either:

(a) coating or encapsulating a carrier material with an aqueous reaction mixture as defined in claim 3, and curing the coating on the material; or

(b) coating a carrier material with a bioadhesive composition as defined in any one of claims 1 to 10.

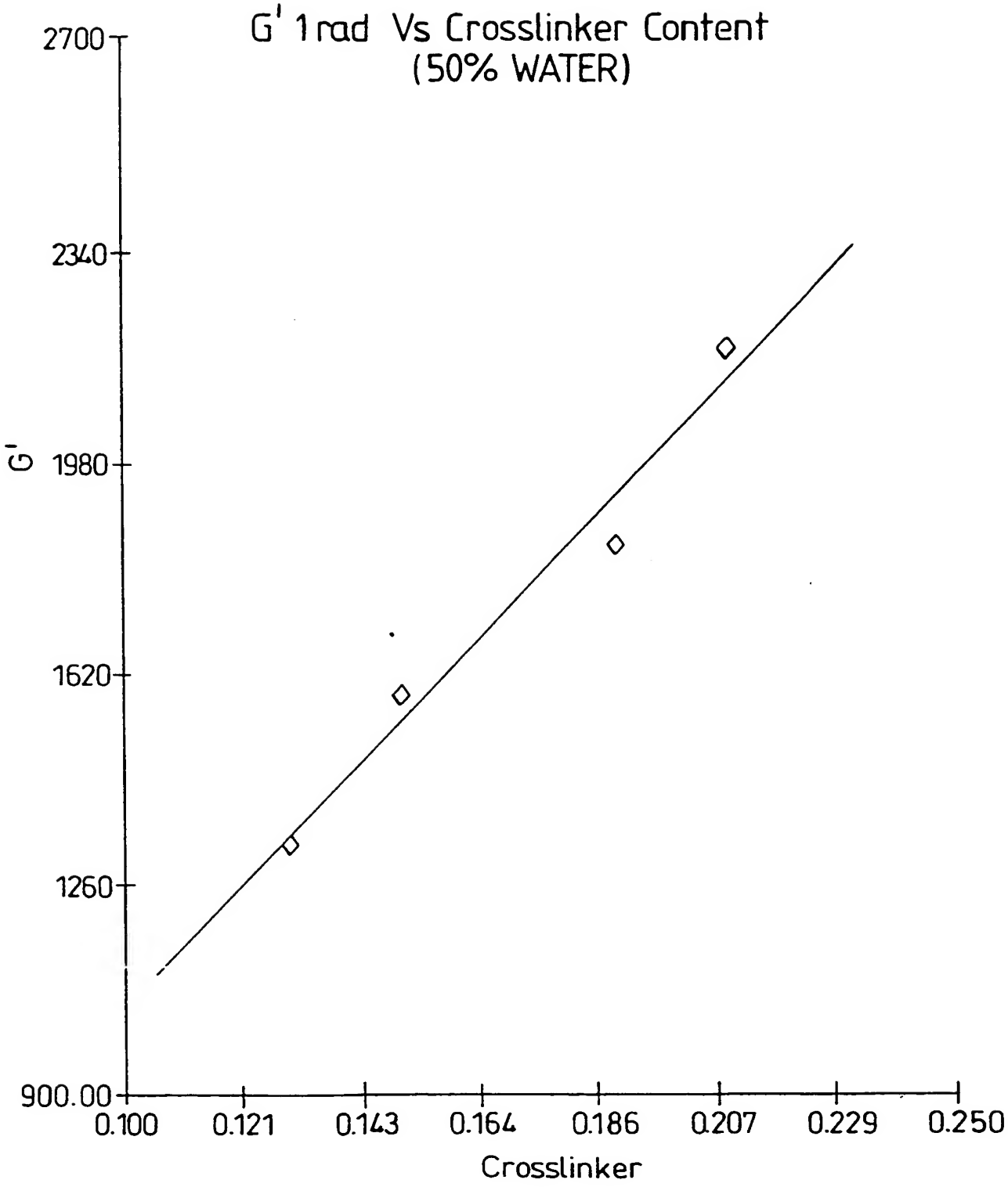


Fig. 1

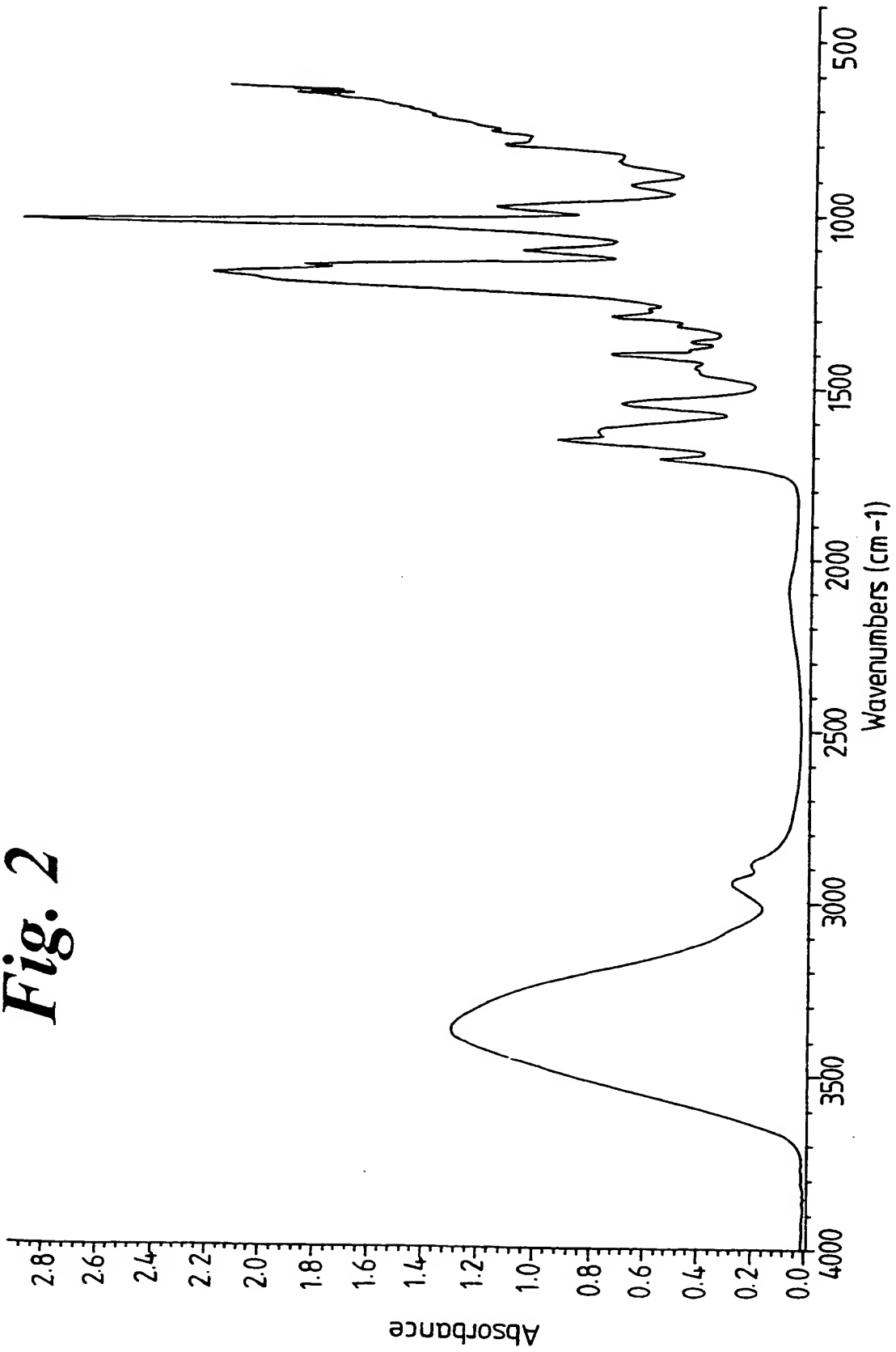


Fig. 2

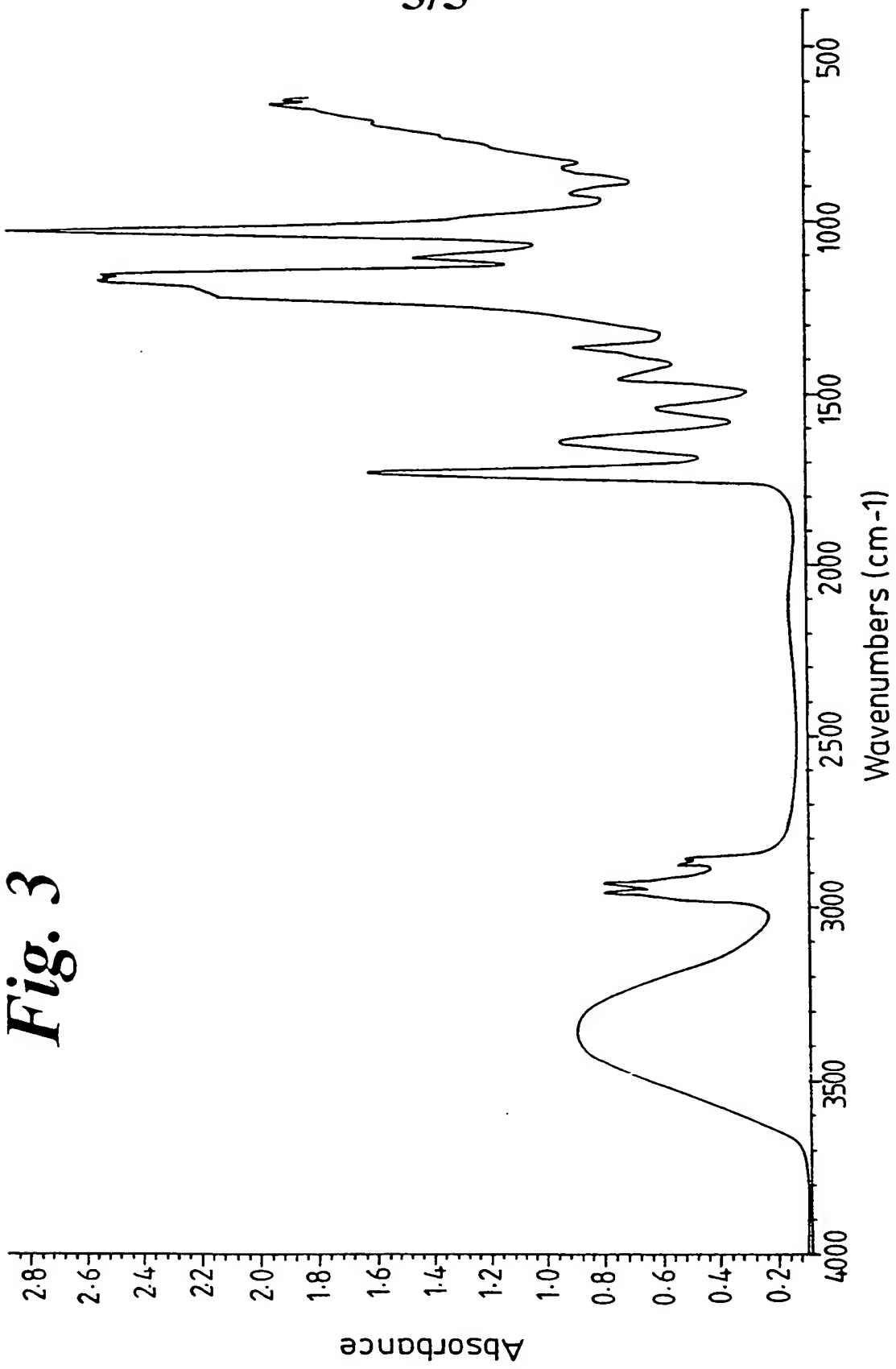


Fig. 3

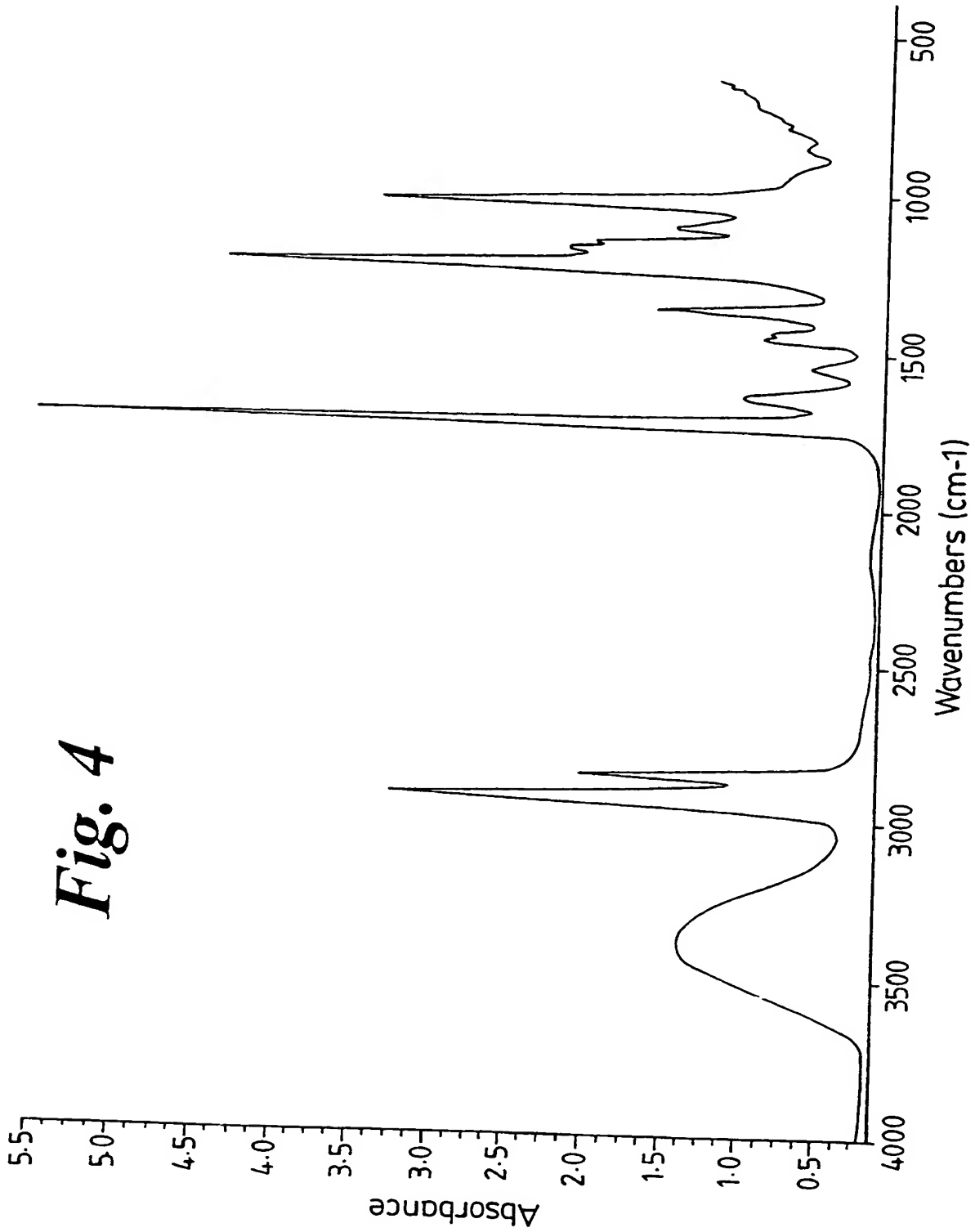


Fig. 4

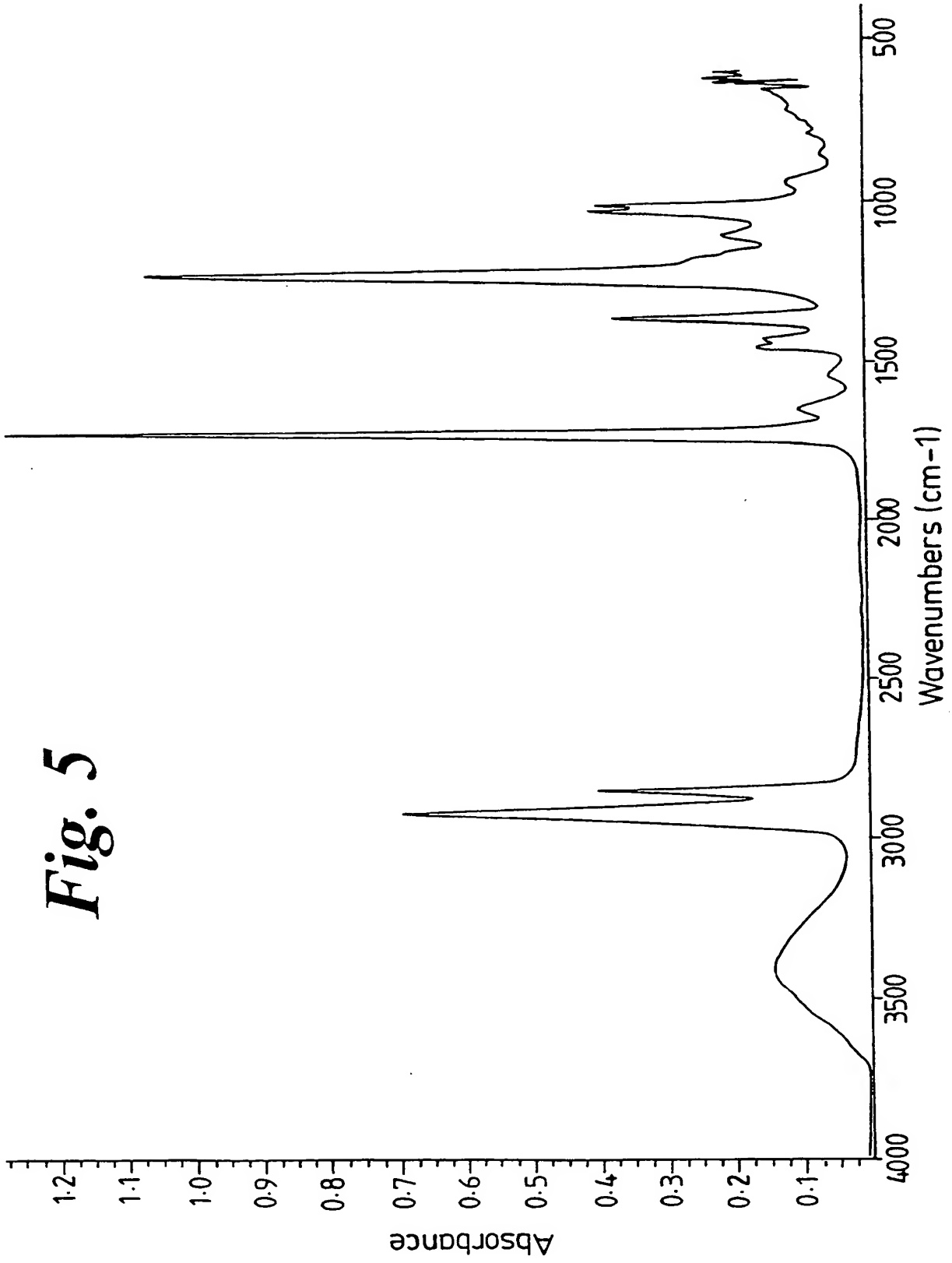


Fig. 5

INTERNATIONAL SEARCH REPORT

Inter: nal Application No
PCT/GB 99/02524

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L15/58 A61L24/06 A61F13/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61F A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	US 5 670 557 A (DIETZ TIMOTHY M ET AL) 23 September 1997 (1997-09-23) column 24, line 66 -column 25, line 48 column 28, line 62 -column 29, line 3 column 30, line 27 - line 31 column 35, line 15 - line 35 --- -/--	1-5, 10-14

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
26 November 1999	07/12/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Menidjel, R

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INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/GB 99/02524

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/GB 99/02524

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